Chronic lymphocytic leukemia (CLL) is characterized by a relentless accumulation of small, mature-appearing monoclonal B-lymphocytes in the blood, marrow, and lymphoid tissue. This accumulation leads to a progressive depression of the patient's immune system with its consequences of myelosuppression and secondary infectious complications. This disease is the most common adult leukemia in the United States, with an average incidence of 2.7 persons per 100.000. Moreover, CLL accounts for approximately 0.8 percent of all cancers and nearly 30 percent of all leukemias at any point in time. Ad-CD154 CLL is intended for use as active immunotherapy of CLL Ex vivo transduced cells that express CD154 are infused i.v. into the original donor. These autologous leukemia cells expressing CD154 are anticipated to induce a strong specific immune activation leading to a therapeutic anti-leukemia immune responses in the host. In this study, the adenovirus vector system is used for ex-vivo modification of autologous CLL B cells. After this ex vivo manipulation, the transduced cells are washed and the amount of remaining free virus will be extensively monitored before the cells are reinfused into the patient. The type of adenovirus to be used in this study is human adenovirus serotype 5 (or Ad5). Infection with Ad5 is frequent in children up to 5 years of age. It is generally not associated with serious illness. In most cases, infection is limited to the upper respiratory tract with or without fever. Retrospective sampling studies of antibody titers to Ad5 show that, depending on the geographic region, from 50% to almost 100% of the population over the age of 5 years have been infected with Ad5. This study will make use of an Ad5 subgroup C adenovirus that lacks the EIA region and has a mutated E3 region. Both of these regions are involved in replication, and therefore this modified virus is unable to replicate in cells lacking expression of these important genes. The use of Ad-CD154 CLL in CLL is not a novel experimental approach. The current Phase II study represents the second in a series of clinical studies using autologous Ad-CD154 expressing transduced CLL cells (Ad-CD154 CLL) in patients with CLL. The initial study (NIH Protocol #9803-242) titled "A Phase I study of CD154 gene-transduced leukemia cells in patients with chronic lymphocytic leukemia" was submitted to the NIH/ORDA for review on March 22. 1998 by Dr. Tom Kipps. The study was initiated during 1998 and enrolled 11 patients who received infusion doses of up to $3x10^9$ total leukemia cells. The study is currently being analyzed, however at present, all patients have received at least a single treatment. with 7 of these patients receiving three or more infusions. Preliminary results suggest that treatment with Ad-CD154 CLL produced a biological effect. In addition, the treatment was well tolerated and no dose-limiting toxicities were observed at the highest dose group of $3x10^9$ total leukemia cells. In the attached Phase II study, patients will be treated with a single infusion of $3-6 x10^8$ autologous Ad-CD154-transduced leukemia cells, Ad-CD154 CLL infused through either peripheral or central venous access. The treatment will be repeated every 2 weeks for at least five infusions for each patient. The primary objective of this study is to determine the extent of tumor load reduction in B-cell CLL patients, as assessed 2 weeks after the fifth infusion of Ad-CD154 CLL. The study will be conducted at 7 different clinical sites in the USA and enroll a total of 60 patients.